UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,108	02/10/2004	Charles R. Ashby JR.	BSA 04-09	2666

26302 7590 08/20/2007

BROOKHAVEN SCIENCE ASSOCIATES/
BROOKHAVEN NATIONAL LABORATORY
BLDG. 475D - P.O. BOX 5000
UPTON, NY 11973

EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
08/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,108	ASHBY, CHARLES R.	
	Examiner	Art Unit	
	Charlesworth Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9, and 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 5/8/07, have been considered but they are not deemed to be fully persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Applicant's statement that the specification has been amended to properly reference the parent patent application, now issued U.S. Patent 6,713,497, from which the instant divisional application claims priority, is acknowledged.

Applicant statement that the novelty of the instant invention is the composition "consisting essentially of gamma vinyl GABA (GVG) and vitamin B6" is acknowledged and made of record. Applicant's assertion that the effect that GVG has on the many chemical reactions of the brain is highly influenced by the presence of other compounds such that the addition of compounds, other than GVG and vitamin B6, to the composition would constitute a material change to the basic and novel characteristics of the invention, is acknowledged and made of record.

This action is made final.

Status of the Claims

Claims 9, and 15-21 are pending in this application and are the subject of the Office action. Claims 1-8, and 10-14 are cancelled; claims 16-21 are new.

Applicant's statement that no new matter has been added by the amendment is acknowledged as well.

Objection

Applicant amendment of the abstract to delete the term "novel" is acknowledged. Applicant's statement that the specification has been amended to capitalize the trademarks which appear on pages 4, 5, 10 and 11, is also acknowledged. Applicant's statement that no new matter has been added is acknowledged and made of record. The objection to the specification is withdrawn.

Summary of rejections

Claims 9, and 15-21 are rejected as being unpatentable over Seiler et al. (US Patent 4,540,582), in view of Evans et al. (US Patent Application Publication No. 2002/0048612) for the reasons stated below in connection with the rejection under 103(a)

Response to Arguments

With respect to the rejection under 112, 2nd Para. (claims 9 and 15)

This rejection is overcome by applicant's amendment of the claims to recite the term "gamma vinyl GABA" is acknowledged. The rejection is therefore withdrawn.

With respect to the rejection under 103(a) (Claims 9 and 15)

Applicant contends the following (see Applicant's Response filed 5/8/07, pages 2-5):

1) the Examiner's characterization of GVG as a "butyrate" or an equivalent thereof is incorrect. Applicant further contends that Evans et al. disclose the use of a "substrate for gamma amino butyric acid (GABA) ... the substrate transformed into GABA within the brain (e.g. page 1, paragraph 0010). Applicant postulates that Evans et al. collectively refer to such compounds as butyrates; however, the term "butyrates" most generally refers to compounds comprising four (4) carbon atoms (e.g. butyric acid = C4H8O2). Applicant contends that gamma vinyl GABA is not a butyrate nor an analog or homolog thereof because it has six (6) carbon atoms (i.e. 4-amino-hex-5-enoic acid). Applicant calls into question the teaching of Evans et al. that butyrates cross the blood brain barrier to encourage the synthesis of GABA (i.e. they are a substrate for gamma amino butyric acid). Applicant asserts that it is well known that

a) GABA is formed by decarboxylation of glutamic acid, and not through incorporation of an amine group onto butyrates, and

b) gamma vinyl GABA (GVG) is not a substrate for GABA ... the substrate transformed into GABA within the brain, and

c) GVG is an irreversible inhibitor of GABA-transaminase, the enzyme that deaminates GABA, thereby generating alpha-ketoglutamate.

2) Evans et al. do teach or suggest that vitamin B6 is a preferred optional ingredient. Applicant postulates that Evans et al disclose "a list of many optional ingredients, possibly hundreds, one of which is vitamin B6. Further, Evans et al. make no reference to GVG. Further, there is no disclosure or suggestion of a composition

consisting essentially of GVG and vitamin B6 (wherein B6 is in an amount of about 50 to 100 mg/day) as taught by the cited prior art references.

3) The combination of Evans et al. and Seiler et al. fail to teach all of the claimed limitations, especially in view of the Examiners's characterization of GVG as a "butyrate" as described by Evans et al.

4) Baxter et al. teaches away from the combination of vitamin B6 plus GVG because the reference discloses that seizures in four patients with West Syndrome that were resistant to GVG (vigabatrin), were responsive to pyridoxine. Applicant postulates that there are no suggestions, findings or teaching that pyridoxine-sensitive seizures could be controlled by treatment with vitamin B6 in combination with GVG. The usual oral dose of 30 mg/kg/day to a maximum dose of 1000 mg/kg/day of vitamin B6 taught by Baxter et al. for control of seizures is substantially higher than that of the instant invention.

5) No teaching, motivation or suggestion in the prior art to created the instant claimed invention.

In response to applicant's arguments identified above as items #1, #2, and #3, it is noted that the argued limitations regarding the definition of a butyrate do not relate to the claimed limitations set forth in the instant claims nor are they supported by the instant specification (see US Patent Application Publication No. 2004/0186144, paragraphs 0017-0027). For instance, applicant discloses that a "GABAergic drug" is any compound that potentiates the GABAergic system or increases GABA levels in the central nervous system (CNS) (see paragraphs 0017-0020) which would reasonably

encompass butyrates regardless of the number of carbon atoms contained in the butytrate molecule.

Evans et al. teach GABA substrate compositions, for example, comprising vitamin B6, L-glutamine, and magnesium butyrate (US Patent Application Publication No. 2002/0048612, paragraph 0012-0020; see also Table 1, page 3). Also, it is noted to the extent that the instant claims are directed to a composition, no patentable weight is being given to the intended use of the composition. Evans et al. teach GABA substrate compositions, including a specific composition, for example, comprising the primary ingredients of vitamin B6, L-glutamine, magnesium butyrate, and other ingredients (US Patent Application Publication No. 2002/0048612, paragraph 0012-0020; see especially, Table 1, page 3); the exemplified composition does not "list hundreds" of optional ingredients as applicant contends. Further, someone of skill in the art at the time the instant invention was made would have deemed it obvious to substitute the known magnesium butyrate, or L-glutamine, ingredient of the butyrate composition taught by Evans et al. with the GVG taught by Seiler et al. (US Patent 4,540,582, col. 2, line 1 to col. 2, line 17; especially Table 1 at col. 7-col. 8; see Office also Office action mailed 2/26/07, page 5) to treat seizures in a patient with a reasonable expectation of success as evidenced by Blum et al. (US Patent (5,189,065).

Blum et al. teach that vitamin B6 is important as a co-factor in the synthesis of dopamine, serotonin and GABA (col. 5, lines 11-12; col. 15, lines 30-32). Blum et al. teach that cocaine addicts often exhibit various nutritional deficiencies and therefore it is preferable to further provide certain vitamins and minerals, particularly pantothenic acid

(B5), pyridoxal phospahe (B6), magnesium, calcium, and zinc (col. 5, lines 7-11). Blum et al. teach that GABA as well as GABA agonists, injected intracereventricularly, will reduce seizure activity during alcohol withdrawal in rodents (col. 4, lines 64-66). Blum et al. teach that GABA concentrations can be increased by the administration, to animals, of the following inhibitors of GABA-T: ethanolamine-P-sulphate, gamma acetylenic GABA, gamma vinyl GABA, gabcucilline, hydrazinopropionic acid, sodium di-N-propylacetate (sodium volproate) and aminooxyacetic acid (inhibitor of vitamin B6) (col. 16, lines 47-55). Blum et al. exemplifies an amino acid formulation comprising pyridoxal phosphate 5mg per capsule, which is administered at a dose of 20 mg per day (col. 16, line 66 to col. 17, line 16, Example 10).

Shashoua (US Patent 5,051,448) teaches pharmacological compositions comprising esters of GABA and esters of GABA analogues and disclose a method of regulating general motor activity in animals, including humans, and to provide a method of preventing and/or treating seizures, epilepsy, and other disorders (col. 3, lines 27-57). Shashoua teaches that amounts of ester derivatives of GABA or GABA analogue useful for promoting the uptake of GABA or GABA analogue by the brain may vary from individual to individual, and can be determined by experimentation as is well understood by those skilled in the pharmaceutical arts (col. 19, lines 21-26). For intravenous injection, amounts in the range of about 1-1000 umol/kg body weight are preferred (col. 19, lines 26-41). Shashoua teaches a method preparing cholesterol gamma-vinyl gamma-aminobutyrate hydrochloride (col. 40, Examples 6 & 7).

Thus, the someone of skill in art at the time the instant invention was made would have found it obvious to create the instant claimed composition consisting essentially of GVG and vitamin B6 with reasonable predictability as both GVG and vitamin B6 are known ingredients of compositions that are used for treating seizures in view of Seiler et al, in view of Evans et al., and as evidenced by the teachings of Blum et al. and Shashoua.

Applicant' s argument identified above as item #4 (that Baxter et al. teach away from the combination of vitamin B6 plus GVG) is not found to be persuasive. In view of the teaching of Baxter et al. (that seizures in four patients with West Syndrome who were resistant to GVG (vigabatrin) were actually responsive to pyridoxine), someone of skill in the art would reasonably be motivated to combine vitamin B6 with GVG, as opposed to using them separately, in order to reduce the level of treatment failures observed with compositions comprising either GVG or vitamin B6 alone. Applicant' s contention that the usual dose of pyridoxine of 30 mg/kg/day to a maximum dose of 1000 mg/kg/day is substantially higher that the dose range of 50 to 100 mg/day is not found to be persuasive in view of fact that the term " *about 50 mg/day to about 100 mg/day,*" as recited in instant claim 9, for example, given its broadest reasonable

possible interpretation, reasonably overlaps with the teaching of Baxter et al. as evidenced by Blum et al. (see Office action mailed 5/18/06, page 6, lines 5-13). Based on applicant's disclosure, an effective amount of vitamin B6 for a human is from about 5 mg/day to about 300 mg/day (paragraph 0041); the lower dosage range as dislosed in the specification (i.e. about 5 mg/day) differs 10 times from the lower dosage limit recited in instant claim (i.e. about 50 mg/day. This same difference if applied to the upper dosage limit of about 100 mg/day, for example, would represent a dose of about 500 mg/day of vitamin B6, rather than 100 mg/day as contended by applicant. Thus, it would have been within the knowledge and skill of someone of skill in the art to optimize the dose amounts of vitamin B6 in the composition to create the instant claimed invention with reasonable predictability.

In response to applicant's above argument identified as item #5, it is stated that the cited prior art references as discussed in the Office action at pages 4-8, and incorporated by reference herein, and discussed above in connection with applicant's arguments under items #1-3, teach/suggest each and every claimed limitation recited in the instant claimed invention. Also, applicant's conclusory statement that there is no specific suggestion or teaching in the references to combine prior art is not found to be persuasive as KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (See the recent Board

decision Ex parte Smith, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 1007, citing KSR, 82 USPQ2d at 1396).

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, and 15-21 are rejected as being unpatentable over Seiler et al. (US Patent 4,540,582), in view of Evans et al. (US Patent Application Publication No. 2002/0048612).

It is noted that the intended use limitations recited in the instant claimed composition (e.g. "...useful for treating seizure disorders in a mammal in need thereof, while mitigating visual field defects;" "...useful for treating drug addiction in a mammal

in need thereof, while mitigating visual field defects;" "wherein the mammal is a human) are not being given patentable weight.

The Office mailed 5/26/07 as it applies to the rejection of claims 9 and 15 under 103(a) is incorporated by reference (see pages 4-8). Also, the above discussion under the Response to Applicant's arguments regarding the rejection under 103(a) is incorporated by reference.

Like claim 9, new claims 16 and 19 recite the limitation *"composition consisting essentially of gamma vinyl GABA and vitamin B6, wherein the vitamin B6 is in an amount of about 50 mg/day to 100mg/day;"* while like claim 15, new claims 17 and 20 recite the limitation *"wherein the gamma vinyl GABA is in an amount of about 100 mg/kg to about 300 mg/kg."*

As discussed on page 5 of the Office action, mailed 2/26/07:

> **Seiler et al. (4,540,582) teach a method for controlling seizures in a patient in need thereof comprising administering to said patient in combination an effective amount of gamma-vinyl GABA, or a pharmaceutically acceptable salt thereof, and an effective amount of glycine, sarcosine (N-methylglycine), or N,N-dimethyl-glycine, or a C1-C8 alkyl ester thereof, or a pharmaceutically acceptable salt thereof. (column 2, lines 1-10). Seiler et al. teach that the term "seizures" includes both convulsive and non-convulsive seizures associated with, for example, epiplesy, trauma, drug withdrawal (e.g. alcohol withdrawal, barbiturate withdrawal, and benzodiazepine withdrawal), tetanus, metabolic disease, elevated body temperature, drug induction**

and porphyria (col. 2, lines 11-17). Seiler et al. teach doses of GVG ranging from 50 mg/kg to 750 mg/kg (col. 6, line 21 to col. 7, line 8).

The limitation *"wherein the gamma vinyl GABA is in an amount of about 100 mg/kg to about 300 mg/kg"* as recited in instant claims 15, 17, and 20, given its broadest reasonable possible interpretation, is construed to overlap with the teaching of Seiler et al. as evidenced by Baxter et al.

As discussed above, the term "composition consisting essentially of gamma vinyl GABA and vitamin B6, wherein the vitamin B6 is in an amount of about 50 mg/day to 100mg/day," given its broadest reasonable possible interpretation, is construed to overlap with the teaching of Seiler et al., in view of Evans et al., as evidenced by Blum et al. and Baxter et al.

Thus, based on the reasons previously made of record, and the further discussions herein, claims 9, and 15-21 are rejected as being obvious in view of Seiler et al. and Evans et al.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

13 August 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER